Docket No.: 7049405002
Customer No. 23,639

Application Serial No. 09/575,377

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REMARKS

Undersigned counsel thanks Examiner Allen for the interview held on July 10, 2006, the substance of which is summarized below. The communication of July 6, 2006 refused entry of the amendment filed April 28, 2006 on grounds that the claims would be directed to a distinct invention from a method from "identifying one or more ion channels of a cell that may be affected by a test substance." Accordingly, the claims submitted herewith are directed to that invention. The amendment filed August 22, 2005 was not entered, so the present changes are based on the claims as they appear in the Amendment filed November 26, 2004. Claims 51 - 73 remain active in the case. Note that claim 73 is not being cancelled this time, in contrast to the amendment filed April 28, 2006 (not entered), because the step of classifying the test substance is not recited in present claim 51. New Claim 74 elaborates on how information on pathways in the cell may be determined using a data library of known compounds which have been classified into one or more functional categories. As such, claim 74 is readable on the elected invention.

Support for reference to a data library formed from known compounds is found on page 30, lines 11 - 12; page 31, lines 7 - 15; page 32, Table 1 and page 33, lines 1 - 17.

Support for the phrase "wherein the deconvolution analysis does not include a spectral analysis that makes use of a Fourier transformation" is on page 13, lines 19 - 21.(..."the present invention's deconvolution software preferably excludes spectral analysis, more specifically a Fourier transformation...")

Serum-free culture medium is supported on page 26, lines 4 - 6 ("The neurons are grown ... in serum-free media. The cells are cultured in defined media...").

An intervening layer acting as a high-impedance seal is supported in the specification at page 11, lines 6 - 12.

Measurement of changes in one or more characteristics selected from after potential, time to cessation of activity, frequency, amplitude, shape, spike rate, or time constant are described on page 40, lines 14 - 31, and this subject matter was also in claim 53.

Deconvoluting changes to identify one or more ion channels affected by the test substance is supported on page 7, lines 13 - 28 and page 10, lines 4 - 16. As claimed, deconvolution exclude spectral analysis making use of a Fourier transformation.

Our initial description of "functional categories" came from the-literature (see ref Riley et al. in the application as well as page 6 lines 17-18) and it is a method of classifying related genes

and their gene products and thus the pathways they enable. We have shown differences in Action Potential peak shape with the data included in the application, see Figure 5.

We have since demonstrated the application in our paper "Toxin Detection Based on Action Potential Peak Shape Analysis using a Realistic Mathematical Model of Differentiated NG106-15 Cells" that has been accepted and is in press in the journal Biosensors and Bioelectronics (Mohan, et al., submitted previously).

Table 1 on page 32 of the application also further illustrates our ability to group the effects of different compounds into different "functional categories."

As discussed on page 40 lines 21-32 and page 41 lines 1-4 of the application, deconvolution of an action potential implies that some prior knowledge of the factors contributing to the shapes are known. It is well known that an action potential requires the contributions of ion fluxes through at least three distinct ion channels. Varying the contributions of these ion fluxes from these channels has been shown to vary the shape of the action potential, and this is illustrated in Figures 5 and 6A of the application. Thus, to deconvolute an action potential into its components and relate them to pathways or functional categories inside a cell requires some prior knowledge of the biology of the system (i.e., a data base of biological test data on the subject cell culture) in order to perform the deconvolution step and identify cell pathways. The Mohan et al. paper illustrates some of our efforts in this area and an implementation of the algorithm shown in Figure 10 of the patent application. This algorithm has been used to deconvolute one of the examples given in Figure 5 of the application and is shown in Figure A below.

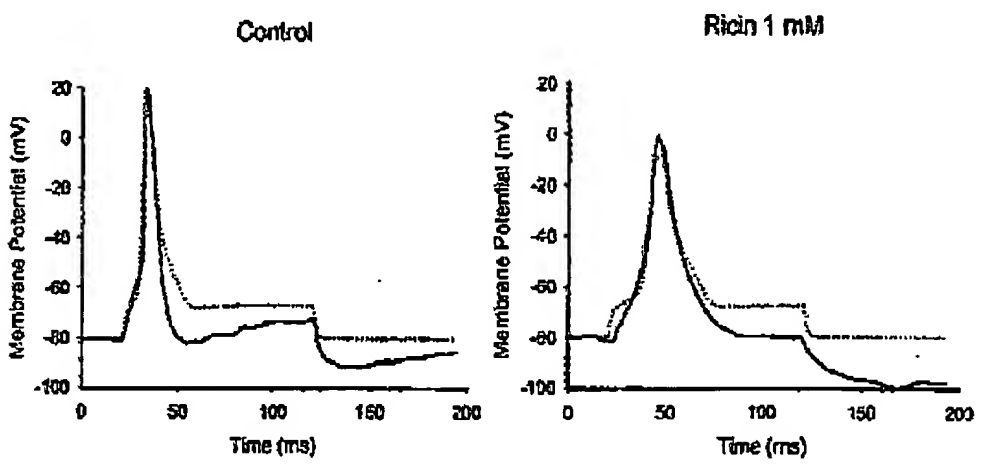

Figure A. Result of parameter fitting to action potential shapes before (left panel) and after (right panel) the application of 1 mM Ricin. Action potentials were recorded from differentiated NG108-15 cells using whole-cell patch clamp method. Action potentials were fitted (dotted lines) with a computer model of NG108-15 cells established based on the measurement of ion channel parameters.

Control	Activation				Inactivation					
		V_{rev}	z	$V_{1/2}$	(	A	z	$V_{1/2}$	(	A
Na	140.00	100.00	6.00	-59.93	-0.45	1.80	-7.48	-7D.36	0.42	8.00
K	26.00	.80.00	8.00	-10.00	-0.60	10.00				
Ca	11.00	32.00	4.10	-11.00	-0.67	0.47				
Ricin										
Na	75.00	100.00	6.00	-59.93	-0.42	3.00	-7.48	-70.36	0.42	12.00
K	26.00	-80.00	8.00	-10.00	-0.60	15.00				
Ca	11.00	32.00	4.10	-11.00	-0.67	0.80				

Table 1. Effect of 1 mM Ricin on the action potential parameters. Action potential parameters were obtained by fitting the parameters of our NG108-15 cell model to the experimental data. 1 mM Ricin caused a significant slow-down of the sodium channel kinetics (parameter A) and a decrease of sodium conductances in the membrane (parameter g). The effect of Ricin on the other ion channels were not so profound, partly because potassium and calcium channels are activated at higher membrane potentials, so their contribution to the Ricin-modified action potential is less (the amplitude of the action potential is smaller, barely reaching 0 mV).

This type of analysis is very different than a spectral analysis, i.e. a Fourier Transform, which arbitrarily assigns combinations of sine waves of different frequencies and amplitudes, to represent the area under a curve. The assignment of the different sine waves is arbitrary and, although it gives a unique signature to a signal, there is no way to relate it to biological information, except through an empirical approach to the testing of drugs or other compounds as well as toxic chemicals.

Claims 51 - 67 and 70 - 73 are rejected under 35 USC 103(a) over Borkholder et al. in view of Georger, Jr. et al.

Borkholder et al. does not specifically disclose an intervening layer, as claimed. Furthermore, it does not disclose or suggest serum-free media. Finally, it does not inherently disclose a deconvolution analysis that does not make use of a Fourier transformation, as claimed. Instead it mentions that a "pattern of spectral changes provides a unique *signature* for the compound. Matching the spectral change pattern of a test compound with the spectral change pattern for reference compounds provides a useful method for characterization of

channel modulating agents." (Col. 4, lines 15 - 20, emphasis added). This passage describes using the observed changes as a fingerprinting method to associate certain channel-modulating compounds with the observed changes, but that is not the same kind of process as deconvoluting a signal to identify the contributions of different ion channels to the signal.

Georger Jr. et al. teaches a method of making biosensors using photolithography placement techniques. It never explicitly states that a high-impedance seal is created or that it would enable deconvolution. For instance, col. 7, lines 58 - 63 does not relate to deconvolution, but at most implies a high-impedance seal. Column 10, lines 58 - 62 describes manual placement, whereas we deposit the cells by cell culture. At col. 13, lines 19 - 24, the cell culture patterning method is to use fewer steps. The discussions at col. 16, line 45 and at col. 10, lines 50 - 65 relate to positioning.

Finally, Georger Jr. et al. uses serum (col. 17, lines 60 - 65) and states at col. 18, lines 9-10 that "adhesion is unaffected by serum." Especially where high-throughput screening is involved, the absence of serum is vital.

Claims 51- 73 are rejected under 35 USC 12, first paragraph, for written description problems. Support for the high-impedance intervening layer allowing deconvolution as claimed is found on page 11, lines 6 - 12.

Claim 51 is rejected under 35 USC 12, first paragraph, on enablement grounds. A positive deconvolution step is now recited.

Claims 51 - 73 are rejected under 35 USC 12, second paragraph, as being indefinite for failure to positively recite a deconvolution step. This has been address by amendment.

Claim 57 has been clarified with respect to the position of the insulator "surrounding" the electrode.

The dependency of claim 61 has been corrected.

Claim *67* does add a limitation over claim *66* because "known function" and "unknown function" are not the only two possibilities for DNA; some DNA has no function at all.

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Applicants submit the case is now in condition for allowance.

Respectfully submitted,

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